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TITLE OF THE INVENTION (280 characters max)

INHIBITORS OF AKT ACTIVITY

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INHIBITORS OF AKT ACTIVITY

FIELD OF THE INVENTION

This invention relates to novel pyridine compounds, the use of such compounds as inhibitors of protein kinase B (PKB or Akt as used herein) kinase activity and in the treatment of cancer and arthritis.

BACKGROUND OF THE INVENTION

The present invention relates to pyridine containing compounds that are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as PKB). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer and arthritis.

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science,* 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science,* 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell,* 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science,* 275:628-630 (1997); Dudek et al., *Science,* 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell,* 81:727-736 (1995); Hemmings *Science,* 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or

dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortrnannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999). It was demonstrated that AKT2 was over-expressed in 12% of ovarian carcinomas and that amplification of AKT was especially frequent in 50% of undifferentiated tumors, suggestion that AKT may also be associated with tumor aggressiveness (Bellacosa, *et al., Int. J. Cancer*, 64, pp. 280-285, 1995). It has also been reported that increased levels of Akt1 activity were detected in primary carcinomas from prostate, breast, and ovary (Sun et al Am. J. Path. 2001, 159 (2), 431-437.

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Nati. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKBα, Akt2/PKBβ, and Akt3/PKBγ respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-

bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKBα occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKBβ and Akt3/PKBγ. The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3 '-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PdtIns(3,4,5)-P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. No specific PDK1 inhibitors have been disclosed. Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

Small molecule inhibitors of AKT are useful in the treatment of tumors with activated AKT (e.g. PTEN null tumors and tumors with ras mutations). PTEN is a critical negative regulator of AKT and its function is lost in many cancers, including breast and prostate carcinomas, glioblastomas, and several cancer syndromes including Bannayan-Zonana syndrome (Maehama, Tomohiko; Taylor, Gregory S.; Dixon, Jack E. *Annual Review of Biochemistry* **2001**, *70*, 247-279), Cowden disease (Parsons, Ramon; Simpson, Laura. *Methods in Molecular Biology (Totowa, NJ, United States)* **2003**, *222(Tumor Suppressor Genes, Volume 1)*, 147-166), and

Lhermitte-Duclos disease(Backman, Stephanie A.; Stambolic, Vuk; Mak, Tak W. *Current Opinion in Neurobiology* **2002**, *12(5)*, 516-522). AKT3 is up-regulated in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer cell lines and AKT2 is over-expressed in pancreatic and ovarian carcinomas. Therefore a small molecule AKT inhibitor is expected to be useful for the treatment of these types of cancer as well as other types of cancer. Small molecule AKT inhibitors are also useful in combination with existing chemotherapeutic agents.

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt/PKB.

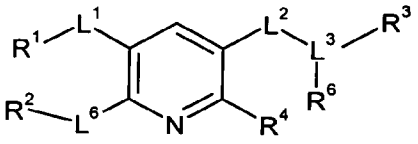
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt/PKB activity.

It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula (I):



(I)

wherein:

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

L^2 is selected from the group consisting of a bond, -O-, -N(R^5)-, -N(R^5)C(O)-, -S-, -S(O)-, -S(O_2)-, and -C(O)N(R^5)-;

L^3 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

L^6 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

R^1 is selected from the group consisting of aryl, substituted aryl, heterocycle and substituted heterocycle;

R^2 is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR^7, -C(O)NR^8R^9, -S(O)$_2$NR^8R^9, and -S(O)$_n$$R^7$,

where n is 0-2,

R^7 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and

R^8 and R^9 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR^{10}, -S(O)$_n$$R^{10}$, -C(O)N$R^{10}R^{11}$, -S(O)$_2NR^{10}R^{11}$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, and substituted aryl,

or R^8 and R^9 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^{10} and R^{11} are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2;

R^3 and R^6 are independently selected from the group consisting of hydrogen, aryl, substituted aryl, and arylalkoxy; provided that when L^1 and L^2 are bonds, at least one of R^3 and R^6 is other than hydrogen;

R^4 is selected from the group consisting of hydrogen and halo; and

R^5 is selected from the group consisting of hydrogen and alkyl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above.

Included among the presently invented compounds of Formula (I) are those having Formula (I):

wherein

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

L^2 is selected from the group consisting of a bond, -O-, -N(R^5)-, -N(R^5)C(O)-, -S-, -S(O)-, -S(O_2)-, and -C(O)N(R^5)-;

L^3 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

L^6 is a bond;

R^1 is selected from the group consisting of aryl, substituted aryl, heterocycle and substituted heterocycle;

R^2 is selected from, cycloalkyl and substituted cycloalkyl;

R^3 and R^6 are independently selected from the group consisting of hydrogen, aryl, substituted aryl, and arylalkoxy; provided that when L^1 and L^2 are bonds, at least one of R^3 and R^6 is other than hydrogen;

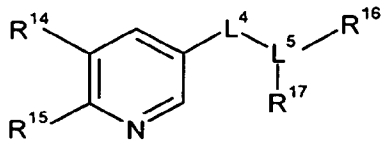
R^4 is selected from the group consisting of hydrogen and halo; and

R^5 is selected from the group consisting of hydrogen and alkyl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed selectively inhibit one, two or the three Akt/PKB isoforms.

Included among the presently invented compounds of Formula (I) are those having Formula (II):



(II) (II)

wherein:

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen;

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl and substituted C_1-C_{12}aryl; and

pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (II) are those in which:

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from phenyl, pyridine, indazole, 7-azaindole, quinoline, isoquinoline, substituted phenyl, substituted pyridine, substituted indazole, substituted 7-azaindole, substituted quinoline and substituted isoquinoline;

R^{15} is selected from cycloalkyl, substituted cycloalkyl, phenyl, pyridine, thiophene, furan, pyrrole, indazole, quinoline, isoquinoline, 7-azaindole, substituted phenyl, substituted pyridine, substituted thiophene, substituted furan, substituted indazole, substituted quinoline, substituted 7-azaindole and substituted isoquinoline; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, phenyl, pyridine, thiophene, furan, pyrrole, substituted phenyl, substituted pyridine, substituted thiophene, substituted furan, and substituted pyrrole; and

pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (II) are those having Formula (II):
wherein

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from cycloalkyl and substituted cycloalkyl; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl and substituted C_1-C_{12}aryl; and

pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the compounds useful in the present invention are:

(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-furan-2-yl-5-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5,6-bis-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-thiophen-2yl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(4-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(3-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-benzyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopent-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopentyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohex-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohexyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(piperidin-4-ylmethoxy)-pyridin-3-yl]-1H-indazole;

3-[5-(3-Methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-propylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-thiophen-2-yl)-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-furan-2-yl)-pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

3-Methyl-5-[2-phenyl-5-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

[(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-chloro-2-thienyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3-aminophenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

(S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy}-ethylamine;

(S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

N-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}-2,6-difluorobenzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}cyclohexanecarboxamide;

[(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol; and

[(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

By the term "aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 1 to 14 carbon atoms and optionally containing from one to five heteroatoms, provided that when the number of carbon atoms is 1 the aromatic ring contains at least four heteroatoms, when the number of carbon atoms is 2 the aromatic ring contains at least three heteroatoms, when the number of carbons is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom.

By the term "C_1-C_{12}aryl" as used herein, unless otherwise defined, is meant phenyl, naphthalene, 3,4-methylenedioxyphenyl, pyridine, biphenyl, indazole, quinoline, isoquinoline, 7-azaindole, pyrimidine, quinazoline, thiophene, furan, pyrrole, pyrazole, imidazole, benzothiophene and tetrazole.

The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the

group consisting of: $-CO_2R^{20}$, aryl, $-C(O)NHS(O)_2R^{20}$, $-NHS(O)_2R^{20}$, hydroxyalkyl, alkoxy, $-C(O)NR^{21}R^{22}$, acyloxy, alkyl, amino, methylamino, dimethylamino, N-acylamino, hydroxy, $-(CH_2)_gC(O)OR^{23}$, $-S(O)_nR^{23}$, $-O(CH_2)_qR^{31}$, $-O(CH_2)_yCH(R^{31})(CH_2)_z(CH_3)$, nitro, tetrazole, cyano, oxo, halogen, and trifluoromethyl;

where

n is 0-2, g is 0-6, q is 1-6, y is 0-6, z is 0-6,

R^{31} is C_1-C_{12}aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R^{23} is hydrogen or alkyl,

R^{20} is selected form hydrogen, C_1-C_4alkyl, aryl and trifluoromethyl, and

R^{21} and R^{22} are independently selected form hydrogen, C_1-C_4alkyl, aryl and trifluoromethyl.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including $-OCH_3$ and $-OC(CH_3)_2CH_3$.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C_3-C_{12}.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl and cyclopentyl.

The term “heterocycle,” as used herein, unless otherwise defined, is meant a cyclic or polycyclic, non-aromatic, three-, four-, five-, six-, or seven-membered ring containing at least one atom, selected from the group consisting of oxygen, nitrogen, and sulfur. The five-membered rings have zero or one double bond and the six- and seven-membered rings have zero, one, or two double bonds.

Examples of heterocyclic groups as used herein include: dihydroisoindolyl, dihydroisoquinolinyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: $-OC(O)CH_3$, $-OC(O)CH(CH_3)_2$ and $-OC(O)(CH_2)_3CH_3$.

By the term "N-acylamino" as used herein is meant a substituent selected from: -N(H)C(O)alkyl, -N(H)C(O)cycloalkyl and -N(H)C(O)aryl; where alkyl and cycloalkyl are as described herein and aryl is C_1-C_{12}aryl as described herein. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH_3, -N(H)C(O)$CH(CH_3)_2$ and -N(H)C(O)$(CH_2)_3CH_3$.

By the term "aryloxy" as used herein is meant -Oaryl where aryl is phenyl, naphthyl, 3,4-methylenedioxyphenyl, pyridyl or biphenyl optionally substituted with one or more substituents selected from the group consisting of: alkyl, hydroxyalkyl, alkoxy, trifuloromethyl, acyloxy, amino, N-acylamino, hydroxy, -$(CH_2)_gC(O)OR^{25}$, -$S(O)_nR^{25}$, nitro, cyano, halogen and protected -OH, where g is 0-6, R^{25} is hydrogen or alkyl, and n is 0-2. Examples of aryloxy substituents as used herein include: phenoxy, 4-fluorophenyloxy and biphenyloxy.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 6 carbon atoms. Examples of alkyl substituents as used herein include: -CH_3, -CH_2-CH_3, -CH_2-CH_2-CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -$(CH_2)_3$-CH_3, -CH_2-$CH(CH_3)_2$, -$CH(CH_3)$-CH_2-CH_3, -CH=CH_2, and -C≡C-CH_3.

By the term "treating" and derivatives thereof as used herein, is meant prophylatic and therapeutic therapy.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

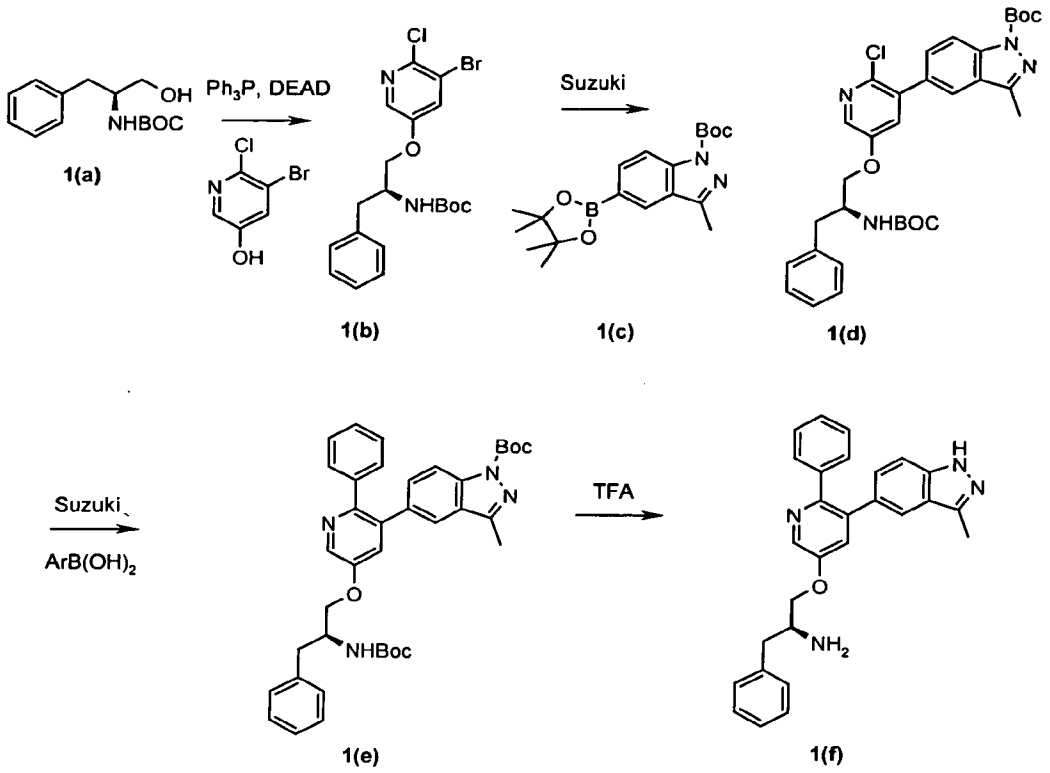
Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

The novel compounds of Formulas I and II are prepared as shown in Schemes 1 through 7 below, or by analogous methods, wherein the 'L' and 'R' substituents are as defined in Formulas I and II respectively and provided that the

'L' and 'R' substituents do not include any such substituents that render inoperative the processes of Schemes 1 through 7. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

Ethers such as **1(b)** can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as N-Boc-(2*S*)-2-amino-3-phenyl-1-propanol (Scheme 1). An aryl moiety such as a 6-(3-methyl-indazole) can be selectively introduced by stoichiometric use of the Suzuki reaction (Pd-mediated cross coupling between aryl boronic acids or aryl boronic esters and aryl halides or triflates) or a Stille reaction (Pd-mediated cross coupling between aryltrialkylstannanes and aryl halides or triflates) to produce intermediates such as **1(d)** (Scheme 1). A second aryl moiety such as a phenyl group can be introduced at the adjacent position on the pyridine by a second Suzuki or Stille reaction forming trisubstituted pyridines such as **1(e)** (Scheme 1). Alternatively, an alkyl or substituted alkyl group such as a benzyl moiety can be introduced by Pd-mediated coupling with an organometallic reagent such as benzyl zinc bromide (Scheme 2) to produce intermediates such as **7(a)**. Alternatively, the Pd-mediated cross coupling steps may precede the etherification or Mitsunobu reaction steps as shown in Scheme 3. Another variant on the synthesis is to introduce alternative linker groups such as amines in place of ethers as exemplified in Scheme 4. For example, ipso-addition of an amine such as 1-(3-pyridinylmethyl)piperazine to a pyridine trifluoromethylsulfonate (triflate or TfO) intermediate such as **16(a)** and elimination under microwave conditions in a solvent such as N-methyl2-pyrollidone (NMP) produces amine analogs such as **16(b)**. In addition, the aryl groups on the substituted pyridine may be further functionalized by further reactions such as acylation of a intermediate amines such as **25(b)** to form amides such **25(c)** as shown in Scheme 5. Final deprotection steps such removal of t-butyloxycarbonyl (Boc) groups with trifluoroacetic acid (TFA) or a solution of hydrochloric acid (HCl) or removal of a carbobenzyloxy (Cbz) by hydrogenolysis with heterogeneous metals.such as Pd on carbon or with a solution of hydrogen bromide (HBr) produces the desired final products such as **1(f)** (Scheme 1), **7(b)** (Scheme 2), **12(d)** (Scheme 3), or **25(d)** (Scheme 5). 3-substituted indazole analogs can be prepared by selective iodination of the parent indazole and Pd-mediated cross coupling steps (Scheme 6). Also, *N*-alkylated analogs of the indazole such as **33(d)** can be prepared by treating intermediate indazoles such as **16(a)** with electrophilic reagents such as Meerwein's reagent followed by a Mitsunobu reaction as described above (Scheme 7).

SCHEME 1



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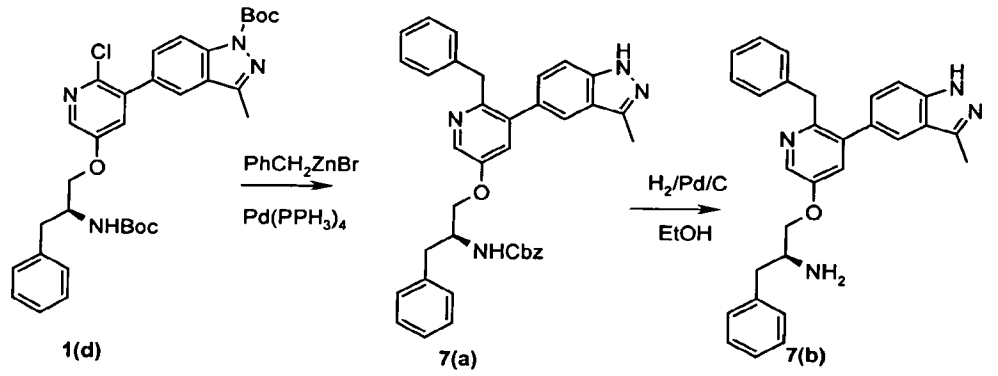

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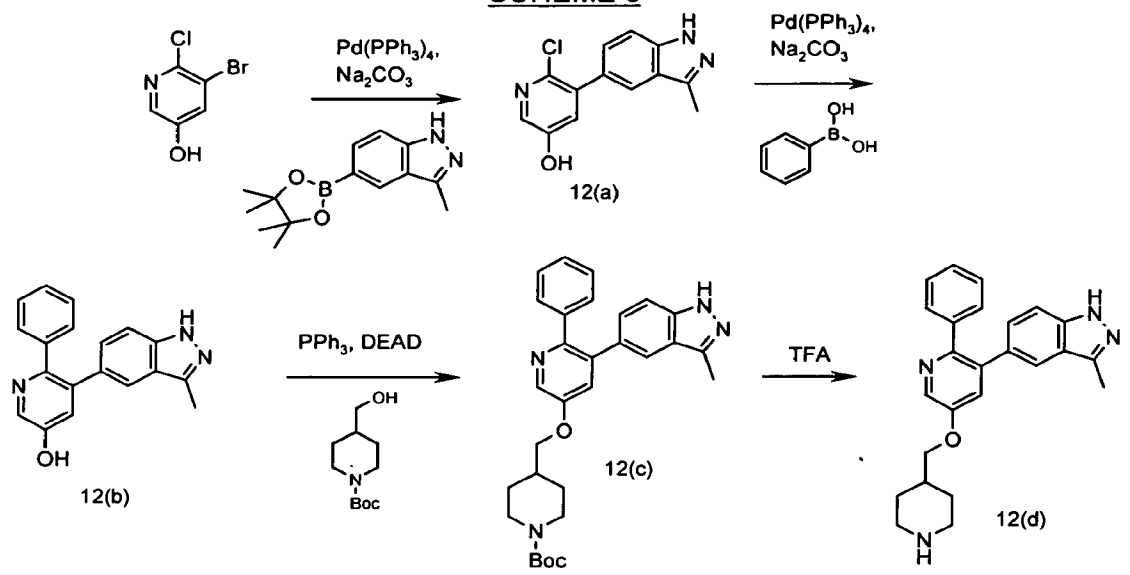
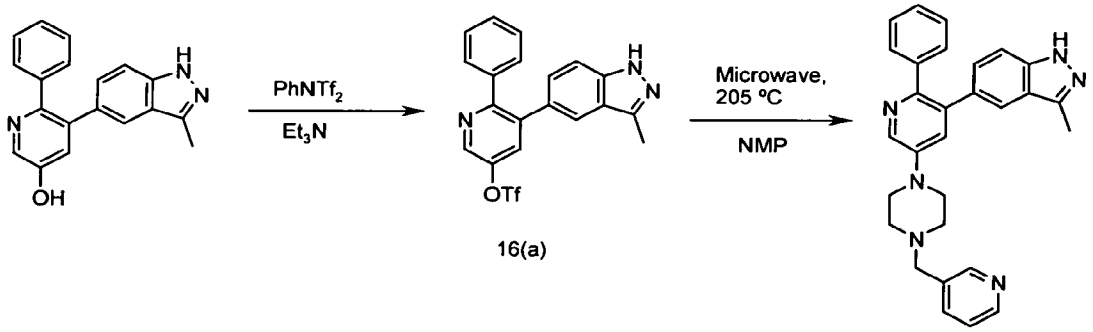
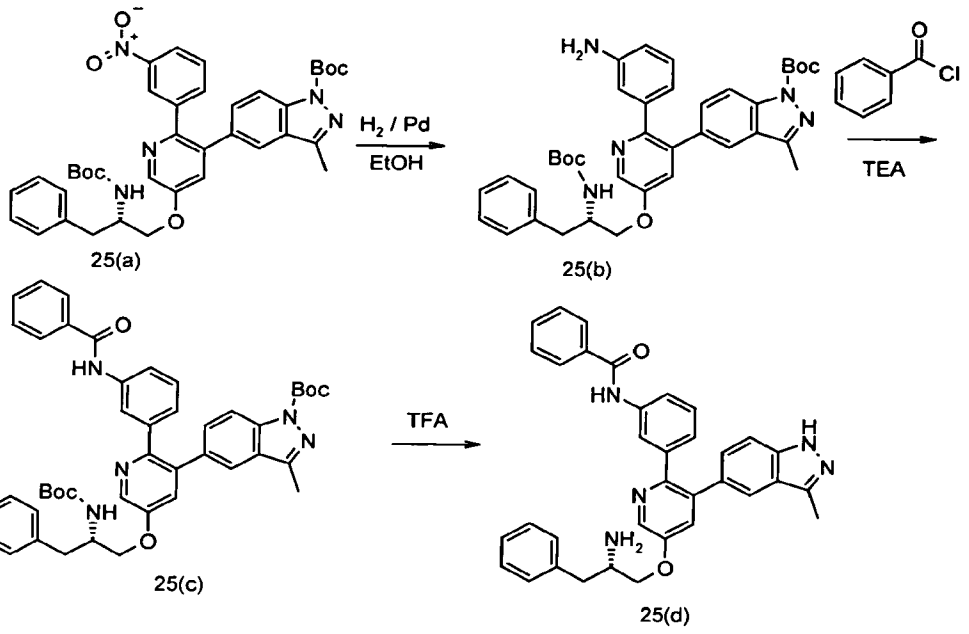


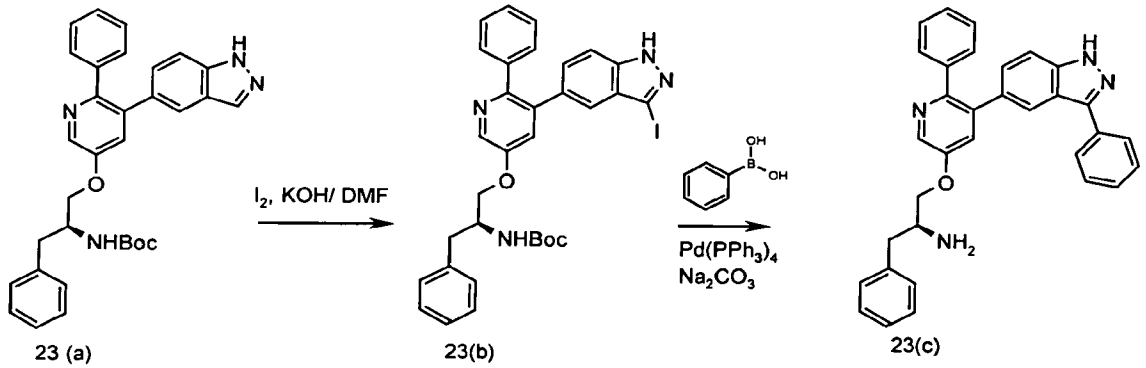
SCHEME 4



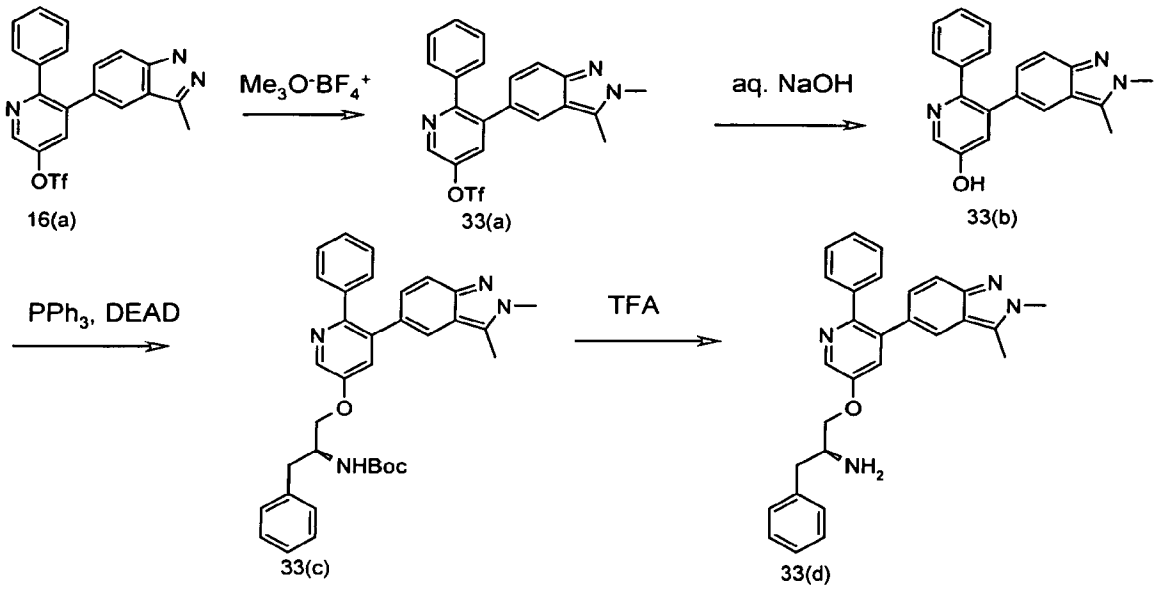
SCHEME 5



SCHEME 6



SCHEME 7



By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Examples of a further active ingredient or ingredients for use in combination with the presently invented AKT inhibiting compounds are chemotherapeutic agents.

Because the pharmaceutically active compounds of the present invention are active as AKT inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from ovarian, pancreatic and prostate.

Isolation and Purification of His-tagged AKT1 (aa 136-480)

Insect cells expressing His-tagged AKT1 (aa 136-480) were lysed in 25 mM HEPES, 100 mM NaCl, 20 mM imidazole; pH 7.5 using a polytron (5 mLs lysis buffer/g cells). Cell debris was removed by centrifuging at 28,000 x *g* for 30 minutes. The supernatant was filtered through a 4.5-micron filter then loaded onto a nickel-chelating column pre-equilibrated with lysis buffer. The column was washed with 5 column volumes (CV) of lysis buffer then with 5 CV of 20% buffer B, where buffer B is 25 mM HEPES, 100 mM NaCl, 300 mM imidazole; pH 7.5. His-tagged AKT1 (aa 136-480) was eluted with a 20-100% linear gradient of buffer B over 10 CV. His-tagged AKT1 (136-480) eluting fractions were pooled and diluted 3-fold with buffer C, where buffer C is 25 mM HEPES, pH 7.5. The sample was then chromatographed over a Q-Sepharose HP column pre-equilibrated with buffer C. The column was washed with 5 CV of buffer C then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl; pH 7.5. His-tagged AKT1 (aa 136-480) containing fractions were pooled and concentrated in a 10-kDa molecular weight cutoff concentrator. His-tagged AKT1 (aa 136-480) was chromatographed over a Superdex 75 gel filtration column pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 1 mM DTT; pH 7.5. His-tagged AKT1 (aa 136-480) fractions were examined using SDS-PAGE and mass spec. The protein was pooled, concentrated and frozen at –80C.

His-tagged AKT2 (aa 138-481) and His-tagged AKT3 (aa 135-479) were isolated and purified in a similar fashion.

AKT Enzyme Assay

Compounds of the present invention were tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation was detected by the following procedure:

Assays were performed in 384well U-bottom white plates. 10 nM activated AKT enzyme was incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM $MgCl_2$, 4uM ATP, 8uM peptide, 0.04 uCi [g-^{33}P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction was stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate was sealed, the beads were allowed to settle overnight, and then the plate was counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses were plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: $y = ((Vmax * x) / (K + x))$ where Vmax is the upper asymptote and K is the IC50.

The pharmaceutically active compounds within the scope of this invention are useful as AKT inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring AKT inhibition, which comprises administering an effective compound of Formula (I) or a pharmaceutically

acceptable salt, hydrate, solvate or ester thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as Akt inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid;. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will

result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Experimental Details

Example 1

Preparation of (S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

a) ((S)-1-Hydroxymethyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester

Saturated $NaHCO_3$ aqueous solution (3 mL) was added to a solution of (-)-phenylalaninol (1.007 g, 6.66 mmol) and di-*t*-butyl dicarbonate (2.18 g, 9.99 mmol) in CH_2Cl_2 and the resulting mixture was stirred at room temperature for 3 h. The reaction was complete indicated by TLC. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined the organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (hexane/EtOAc 3:1) to give a white solid (1.64 g , 98%).

b) 3-Bromo-2-chloro-5-((S)-2-methyl-3-phenyl-propoxy)-pyridine

DEAD (0.30 mL, 1.87 mmol) was added to a solution of 4-bromo-5-chloro-3-hydroxypyridine (243 mg, 1.17 mmol, Koch, V. Schnatterer, S. *Synthesis*, **1990**, 499-501), compound of Example 1 (a) (440 mg, 1.80 mmol) and Ph_3P (460 mg, 1.80 mmol) in THF (10 mL) at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 1 h. The reaction was complete indicated by TLC. The reaction mixture was concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 9:1) to give a white solid (450 mg, 87%).

c) 3-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester

A mixture of N-Boc-3-methyl-5-bromoindazole (1.11 g, 3.58 mmol), bis(pinacola)diboron (1.0 g, 3.94 mmol), KOAc (527 mg, 5.37mmol), Pd_2dba_3 (49 mg, 0.054 mmol) and PCy_3 (72 mg, 0.26 mmol) in dioxane (21.5 mL) was purged with N_2 and heated at 80 °C under N_2 for 24 h. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 9:1) to give a light yellow solid (1.046 g, 74%).

d) 5-[5-((S)-2- *tert* -Butoxycarbonylamino-3-phenyl-propoxy)-2-chloro-pyridin-3-yl]-3-methyl-indazole-1- carboxylic acid *tert*-butyl ester

A mixture of the compound of Example 1(b) (550 mg, 1.24 mmol), compound of Example 1(c) (550 mg, 1.53 mmol), $(Ph_3P)_4Pd$ (143 mg, 0.12 mmol), 2N Na_2CO_3 aqueous solution (0.84 mL) and 1,4-dioxane (10 mL) was degassed and heated at 100 °C under N_2 overnight. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 3:1 to 1:1) to give a light yellow solid (585 mg, 80%).

e) {(S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethyl}-carbamic acid *tert* -butyl ester

A mixture of the compound of Example 1(d) (196 mg, 0.33 mmol), phenylboronic acid (80.6 mg, 0.66 mmol), $(Ph_3P)_4Pd$ (19 mg, 0.016 mmol), 2N Na_2CO_3 aqueous solution (0.73 mL) and 1,4-dioxane (3 mL) was degassed and irradiated under microwave at 160 °C for 20 min. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined the filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 3:1 to 1:1) to give a light yellow solid (101 mg, 57%).

f) (S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

A solution of the compound of Example 1(e) and 0.5 mL of TFA in CH_2Cl_2 (1.5ml) was stirred at room temperature for 30 min, diluted with toluene and concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (78mg,78%). ^1H NMR (CD_3OD, 400 MHz) δ 8.49 (d, *J* = 2.8 Hz, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.66 (d, *J* = 0.7 Hz, 1H), 7.40-7.32 (m, 11H), 7.11 (dd, *J* = 8.7, 1.6 Hz), 4.46 (dd, *J* = 10.6, 3.0 Hz, 1H), 4.31 (dd, *J* = 10.6, 5.6 Hz, 1H), 4.03-3.95 (m, 1H), 3.19 (d, *J* = 7.4 Hz, 2H), 2.50 (s, 3H); MS (M+H): 435.2

Example 2

Preparation of (S)-1-Benzyl-2-[6-furan-2-yl-5-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 2-furanboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.40 (d, *J* = 2.8 Hz, 1H), 7.72 (dd, *J* = 1.4, 0.9 Hz, 1H), 7.61 (d, *J* = 2.8 Hz, 1H), 7.56-7.54 (m, 2H), 7.41-7.31 (m, 7H), 7.28 (dd, *J* = 8.6,

1.6 Hz, 1H), 6.36 (dd, J = 3.5, 1.8 Hz, 1H), 5.91 (dd, J = 3.5, 0.6 Hz, 1H), 4.48 (dd, J = 10.6, 3.0 Hz, 1H), 4.23 (dd, J = 10.6, 5.6 Hz, 1H), 4.00-3.90 (m, 1H), 3.16 (d, J = 7.6 Hz, 2H), 2.58 (s, 3H); MS (M+H): 425.2

Example 3

Preparation of (S)-1-Benzyl-2-[5,6-bis-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting the compound of Example 1(c) for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (s, 1H), 7.81-7.78 (m, 2H), 7.71 (s, 1H), 7.40-7.27 (m, 13H), 7.19 (dd, J = 8.7, 1.5 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 4.45-4.42 (m, 1H), 4.30-4.25 (m, 1H), 4.01-3.92 (m, 1H), 3.19 (d, J = 6.7Hz, 2H), 2.50 (s, 3H), 2.45 (s, 3H) MS (M+H): 489.2

Example 4

Preparation of (S)-1-Benzyl-2-[6-thiophen-2yl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 2-thiopheneboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47 (d, 1H), 7.90 (s, 1H), 7.68 (d, 1H), 7.48-7.30 (m, 8H), 7.17 (d, 1H), 6.88 (dd, 1H), 4.45 (dd, 1H), 4.32 (dd, 1H), 4.00 (m, 1H), 3.19 (d, 2H), 2.54 (s, 3H). MS (M+H): 441.2

Example 5

Preparation of (S)-1-Benzyl-2-[6-(4-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 4-chlorophenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H), 7.68 (dd, 2H), 7.40-7.29 (m, 6H), 7.22 (m, 4H), 7.06 (m, 1H), 4.40 (dd, 1H), 4.25 (dd, 1H), 3.99-3.95 (m, 1H), 3.19 (d, 2H), 2.53 (s, 3H). MS (M+H): 469.2

Example 6

Preparation of (S)-1-Benzyl-2-[6-(3-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 3-chlorophenylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.42 (d, 1H), 7.65 (s, 1H), 7.60 (s, 1H), 7.42-7.28 (m, 8H), 7.19 (t, 1H), 7.08 (m, 2H), 4.39 (dd, 1H), 4.26 (dd, 1H), 3.97 (m, 1H), 3.18 (d, 2H), 2.50 (s, 3H). MS (M+H): 469.2

Example 7

Preparation of (S)-1-Benzyl-2-[6-benzyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

a) {(S)-1-Benzyl-2-[6-benzyl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethyl}-carbamic acid benzyl ester

A mixture of 1(d) (35 mg, 0.059 mmol), BrZnPh (0.59 mL, 0.5 M in THF), and $Pd(Ph_3P)_4$ (6.8 mg, 0.0059 mmol) was purged with N_2, stirred at 75 °C overnight and cooled to room temperature. Saturated NH_4Cl aqueous solution was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a mixture of 7(a) and {(s)-1-Benzyl-2-[6-chloro-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethyl}-carbamic acid benzyl ester (18mg).

b) (S)-1-Benzyl-2-[6-benzyl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine

A mixture of 7(a) and {(s)-1-Benzyl-2-[6-chloro-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethyl}-carbamic acid benzyl ester (18 mg), 10% Pd/C (5 mg) and 0.5 mL of MeOH was stirred under a balloon pressure of H_2 overnight. The reaction mixture was filtered through celite, which was rinsed with MeOH. The combined filtrates were concentrated and the residue was purified by reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give 2.3 mg of the title compound. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.40 (d, 1H), 7.62 (dd, 1H), 7.53 (d, 1H), 7.46 (s, 1H), 7.40-7.27 (m, 6H), 7.18 (m, 3H), 6.88 (m, 2H), 4.35 (dd, 1H), 4.20 (m, 3H), 3.82 (m, 1H), 3.13 (d, 2H), 2.49 (s, 3H), MS (M+H): 449.2

Example 8

Preparation of (S)-1-Benzyl-2-[6-cyclopent-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting cyclopent-1-enylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H), 8.14 (d, 1H), 7.86 (s, 1H), 7.60 (d, 1H), 7.53-7.38(m, 6H), 6.30 (s, 1H), 4.49 (dd, 1H), 4.34 (dd, 1H), 4.00 (m, 1H), 3.17 (d, 2H), 2.60 (s, 3H), 2.52 (m, 2H), 2.24 (m, 2H), 1.90 (m, 2H), MS (M+H): 425.4

Example 9

Preparation of (S)-1-Benzyl-2-[6-cyclopentyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

To the solution of Example 8 (7.8 mg, 0.012 mol) in MeOH (0.5 ml) was added 5 mg of 10% Pd/C. The mixture was stirred under a balloon pressure of H_2 for 1 hr. The reaction mixture was filtered through celite, which was rinsed with MeOH. The combined filtrates were concentrated and the residue was purified by reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give 6 mg (77%) of the title compound. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1H), 8.05 (d, 1H), 7.80 (s, 1H), 7.65 (dd, 1H)7.55-7.29 (m, 6H), 4.44-4.40 (dd, 1H), 4.30-4.26 (dd, 1H), 3.97 (m, 1H), 3.54-3.45 (m, 1H), 3.15 (d, 2H), 2.61 (s, 3H), 2.10-1.59 (m, 8H), MS (M+H): 427.4

Example 10

Preparation of (S)-1-Benzyl-2-[6-cyclohex-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting cyclohex-1-enylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.44 (d, 1H), 8.25 (d, 1H), 7.90 (s, 1H), 7.62 (d, 1H), 7.53 (d, 1H), 7.42-7.30 (m, 5H), 6.27 (t, 1H), 4.49 (m, 1H), 4.35 (m, 1H), 4.00 (m, 1H), 3.17 (d, 2H), 2.61 (s, 3H), 2.26 (m, 2H), 1.83 (m, 2H), 1.61 (m, 2H), 1.53 (m, 2H). MS (M+H): 439.2

Example 11

Preparation of (S)-1-Benzyl-2-[6-cyclohexyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine

Following the procedure of Example 9, except substituting Example 8 with Example 10, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.41 (d, 1H), 7.83 (d, 1H), 7.74 (s, 1H), 7.63 (d, 1H), 7.40-7.29 (m, 6H), 4.41(dd, 1H), 4.24 (dd, 1H), 3.96 (m, 1H), 3.14 (d, 2H), 2.98 (m, 1H), 1.90-1.62 (m, 7H), 1.48-1.11 (m, 3H). MS (M+H): 441.2

Example 12

Preparation of 3-Methyl-5-[2-phenyl-5-(piperidin-4-ylmethoxy)-pyridin-3-yl]-1H-indazole

a) 6-chloro-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinol

A mixture of 5-bromo-6-chloro-3-pyridinol (1.40 g, 6.70 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (2.08 g, 8.04 mmol), $(Ph_3P)_4Pd$ (385 mg, 0.34 mmol), 2N Na_2CO_3 aqueous solution (7.7 mL) and DME (20 mL) was degassed and heated at 80 °C under N_2 overnight. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a light yellow foamy solid (1.23 g, 71%).

b) 5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinol

A mixture of compound of Example 12(a) (1.03 g, 4.75 mmol), phenylboronic acid (695 mg, 5.70 mmol), $(Ph_3P)_4Pd$ (274 mg, 0.24 mmol), 2N Na_2CO_3 aqueous solution (8.5 mL) and 1,4-dioxane (20 mL) was degassed and heated at 100 °C overnight. The reaction mixture was filtered through celite, which was rinsed with EtOAc. The combined the filtrates were concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a light yellow solid (846 mg, 70%).

c) 1,1-dimethylethyl 4-({[5-(3-methyl-1*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}methyl)-1-piperidinecarboxylate

DEAD (0.033 mL, 0.2mmol) was added to a solution of the compound of Example 12(b) (40 mg, 0.13 mmol), 1,1-dimethylethyl 4-(hydroxymethyl)-1-piperidinecarboxylate (42.8mg, 0.2mmol) and Ph_3P (52 mg, 0.2 mmol) in THF (1 mL) at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 1 h. The reaction was complete indicated by TLC. The reaction mixture was concentrated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1) to give a white solid (45 mg, 69%).

d) 3-methyl-5-{2-phenyl-5-[(4-piperidinylmethyl)oxy]-3-pyridinyl}-1*H*-indazole

A solution of compound of Example 12(c) and 0.5 mL of TFA in CH_2Cl_2 (1.5ml) was stirred at room temperature for 30 min, diluted with toluene and concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (35 mg, 62%). ^1H NMR (CD_3OD, 400 MHz) δ 8.56 (d, 1H), 8.23 (d, 1H), 7.74 (s, 1H), 7.52-7.35 (m, 6H), 7.13 (d, 1H), 4.27 (d, 2H), 3.50 (d, 2H), 3.12 (m, 2H), 2.51 (s, 3H), 2.30 (m, 1H), 2.17 (d, 2H), 1.73 (m, 2H), MS (M+H): 399.4

Example 13

Preparation of 3-[5-(3-Methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-propylamine

Following the procedure of Example 12, except substituting (2-Hydroxy-ethyl)-carbamic acid tert-butyl ester for 1,1-dimethylethyl 4-(hydroxymethyl)-1-piperidinecarboxylate the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.57 (d, 1H), 8.25 (d, 1H), 7.74 (s, 1H), 7.50-7.34 (m, 6H), 7.15 (d, 1H), 4.78 (t, 2H), 3.26 (t, 2H), 2.50 (s, 3H), 2.30 (m, 2H), MS (M+H): 359.2

Example 14

Preparation of (S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-thiophen-2-yl)-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 5-methylthiophen-2-ylboronic acid for phenylboronic acid, the title compound was prepared. ^1H NMR (CD_3OD, 400 MHz) δ 8.31(d, 1H), 7.70 (s, 1H), 7.51 (d, 1H), 7.49-7.24 (m, 7H), 6.47 (m, 1H), 6.31 (d, 1H), 4.31 (dd, 1H), 4.17 (dd, 1H), 3.95 (m, 1H), 3.15 (d, 2H), 2.57 (s, 3H), 2.39 (s, 3H). MS (M+H): 455.0

Example 15

Preparation of (S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-furan-2-yl)-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 5-methylfuran-2-ylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.37(s, 1H), 7.70 (m, 2H), 7.62 (m, 1H), 7.49-7.30 (m, 5H), 5.97 (m, 1H), 5.80 (s, 1H), 5.73 (s, 1H), 4.37 (dd, 1H), 4.22 (dd, 1H), 3.96 (m, 1H), 3.17 (d, 2H), 2.55 (s, 3H), 2.26 (s, 3H). MS (M+H): 439.2

Example 16

Preparation of 3-Methyl-5-[2-phenyl-5-(4-pyridin-3-yl-methyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole

a) Trifluoro-methanesulfonic acid 5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yl ester

A solution of compound 12(b) (150 mg, 0.50 mmol) and $PhNTf_2$ (213 mg, 1.2 eq.) in CH_2Cl_2 (5 mL) was added Et_3N (0.14 mL, 2.0 eq.). The resulting mixture was stirred at rt overnight, washed with water, brine, and dried (Na_2SO_4). Removal of the solvent followed by flash column chromatography of the residue on silica gel afforded 198 mg (92%) of the titled compound.

b) 3-Methyl-5-[2-phenyl-5-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole

A solution of compound Example 16(a) (13.8 mg, 0.032 mmol) and 1-pyridin-3-ylmethyl-piperazine (14 mg, 2.5 eq.) in NMP (0.2 mL) was irradiated with microwave (personal choice synthesizer) at 205 °C for 30 min. The reaction mixture was loaded on the reversed phase HPLC column and purified (MeCN, H_2O, 0.1% TFA) to give 17.2 mg of white solid (67%). ^{1}H NMR (CD_3OD, 400 MHz) δ 9.04 (s, 1H), 8.90 (s, 1H), 8.58 (d, 1H), 8.46 (s, 1H), 8.26 (s, 1H), 8.00 (m, 1H), 7.77 (s, 1H), 7.50-7.34 (m, 6H), 7.15 (d, 1H), 4.59 (s, 2H), 3.88 (t, 4H), 3.51 (t, 4H), 2.51 (s, 3H). MS (M+H): 461.4

Example 17

Preparation of 3-Methyl-5-[2-phenyl-5-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole

Following the procedure of Example 16, except substituting 1-pyridin-4-ylmethyl-piperazine for 1-pyridin-3-ylmethyl-piperazine the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.88(d, 2H), 8.41 (d, 1H), 8.21 (d, 1H),

8.13 (d, 2H), 7.76 (s, 1H), 7.48-7.34 (m, 6H), 7.12 (d, 1H), 4.31 (s, 2H), 3.78 (t, 4H), 3.15 (t, 4H), 2.51 (s, 3H). MS (M+H): 461.4

Example 18

Preparation of [(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 3-furanboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.39 (d, *J* = 2.4 Hz, 1H), 7.72 (s, 1H), 7.57 (s, 1H), 7.53(d, *J* = 8.8 Hz, 1H), 7.41-7.15 (m, 8H), 6.31(dd, *J* = 3.5, 1.8 Hz, 1H), 4.36 (d, *J* = 10.4, 1H), 4.22 (dd, *J* = 10.6, 5.6 Hz, 1H), 4.00-3.94 (m, 1H), 3.16 (m, 2H), 2.57 (s, 3H); MS (M+H): 425.2.

Example 19

Preparation of [(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-chloro-2-thienyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting 5-chloro-2-thiopheneboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.33 (d, 1 H), 7.16 (d, 1 H), 7.49 (d, 1 H), 7.41-7.28 (m, 6 H), 7.26 (d, 1 H), 6.92 (d, 1 H), 6.46 (d, 1 H), 4.32 (dd, 1 H), 4.18 (dd, 1 H), 3.95 (m, 1 H), 3.14 (m, 2 H), 2.58 (s, 3 H), 2.01 (s, 3 H); MS (M+H): 475.2/ 477.2.

Example 20

Preparation of [(1*S*)-2-{[6-(3-aminophenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting (3-aminophenyl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1 H), 7.65 (m, 2 H), 7.42-7.22 (m, 10 H), 7.11 (d, 1 H), 4.39 (m, 1 H), 4.26 (dd, 1 H), 3.98 (m, 1 H), 3.19 (m, 2 H), 2.52 (s, 3 H); MS (M+H): 449.4.

Example 21

Preparation of (S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester for compound Example 1(C), the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.53 (d, 1 H), 8.06 (s, 1H), 7.98 (d, 1H), 7.75 (s, 1H), 7.46-7.30 (m, 10 H), 7.13 (d, 1 H), 4.49 (dd, 1 H), 4.33(dd, 1 H), 4.01(m, 1 H), 3.19(d, 2 H); MS (M+H): 421.2.

Example 22

Preparation of (S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy}-ethylamine

a) 2-[3-(3-fluoro-benzyloxy)phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

A mixture of 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (110 mg, 0.50 mmol), 3-fluorobenzyl bromide (0.074 mL, 1.2 eq.), Cs_2CO_3 (179 mg, 1.1 eq) and DMF (3 mL) was stirred at rt for 3 hr, and taken up into EtOAc and water. The organic was separated, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel to give 91 mg (55%) of the titled compound.

b) (S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy}-ethylamine

Following the procedure of Example 1(a)-1(f), except substituting compound of Example 22 (a) for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46 (s, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 7.40-6.87 (m, 15H), 4.85 (s, 2H), 4.45 (dd, 1H), 4.29 (dd, 1H), 3.99 (m, 1H), 3.18 (d, 2H), 2.52 (s, 3H); MS (M+H): 559.4

Example 23

Preparation of (S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

a) {(S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethyl}-carbamic acid tert-butyl ester

Following the procedure of Example 1(a)-1(e), except substituting 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indazole-1-carboxylic acid tert-butyl ester for the compound of Example 1(c), the title compound was prepared.

b) {(S)-1-Benzyl-2-[5-(3-iodo-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethyl}-carbamic acid tert-butyl ester

Iodine (53 mg, 1.5 eq.) and KOH (20 mg, 2.5 eq., grounded) were added to a solution of the compound of Example 23(a) (71 mg, 0.14 mmol) in DMF (1.5 mL). The reaction mixture was stirred at rt for 30 min, and taken up into EtOAc and water. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (2:1 hexane/EtOAc) to give a white solid (37 mg, 42%).

c) (S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine

Following the procedure of Example 1(e), except substituting compound of Example 23(b) for compound of Example 1(d), the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.54 (d, 1H), 8.04 (d, 1H), 7.81 (s, 1H), 7.65-7.29 (m, 17H), 4.49 (dd, 1H), 4.36-4.32 (m,1H), 4.03-3.99 (m, 1H), 3.20 (d, 2H); MS (M+H): 497.2.

Example 24

Prepatation of [(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 1(a)-1(f), except substituting (1-{[(1,1-dimethylethyl)oxy]carbonyl}-1*H*-pyrrol-2-yl)boronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.35 (d, 1 H), 7.71 (s, 1 H), 7.59 (d, 1 H), 7.52 (d, 2 H), 7.40-7.25 (m, 7 H), 6.82 (d, 2 H), 5.98 (m, 1 H), 5.65 (m, 1 H), 4.35 (dd, 1 H), 4.21 (dd, 1 H), 3.95 (m, 1 H), 3.20 (d, 2 H), 2.67 (s, 3 H); MS (M+H): 424.2.

Example 25

Prepatation of *N*-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide

a) {(S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-(3-nitro-phenyl)-pyridin-3-yloxy]-ethyl}-carbamic acid *tert* -butyl ester

Following the procedure of Example 1(a)-1(e), except substituting 3-nitrophenylboronic acid for phenylboronic acid, the title compound was prepared.

b) {(S)-1-Benzyl-2-[5-(3-methyl-1 *H* -indazol-5-yl)-6-(3-amino-phenyl)-pyridin-3-yloxy]-ethyl}-carbamic acid *tert* -butyl ester

To a solution of the compound of Example 25(a) (260mg, 0.38mmol) in EtOH was added 10% Pd/C (26mg) and the reaction mixture was stirred under a H_2 balloon overnight. The reaction mixture was filtered through celite, which was rinsed with EtOH. The combined filtrates were concentrated to give the titled product (240mg, 97%).

c) *N*-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide

A solution of the compound of Example 25(b) (90mg, 0.14mmol), benzoyl chloride (30mg, 0.21mmol) and TEA (0.04ml, 0.28mmol) in 3ml CH_2Cl_2 was stirred at rt for 20min. Solvent was removed and the residue was dissolved in EtOAc, which was washed with $NaHCO_3$, brine and dried. Removal of the solvent followed by flash column chromatography purification of the residue on silica gel afforded the titled compound (78mg, 75%).

d*)* *N*-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}benzamide

A solution of the compound of Example 25(c) (78mg, 0.10mmol) in 0.6ml TFA and 2ml CH_2Cl_2 was stirred at rt for 20 min, diluted with toluene, and concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (40mg, 72%). ^1H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1 H), 7.93 (s, 1 H), 7.86 (m, 2 H), 7.75 (d, 1 H), 7.67 (s, 1 H), 7.62-7.45 (m, 4 H), 7.40-7.30 (m, 6 H), 7.22 (t, 1 H), 7.16 (d, 1 H), 6.98 (d, 1 H), 4.45 (dd, 1 H), 4.29 (dd, 1 H), 4.02 (m, 1 H), 3.18 (d, 2 H), 2.52 (s, 3 H); MS (M+H): 553.2.

Example 26

Prepatation of *N*-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}-2,6-difluorobenzamide

Following the procedure of Example 25, except substituting 2,6-difluorobenzoyl chloride for benzoyl chloride, the title compound was prepared.

^{1}H NMR (CD_3OD, 400 MHz) δ 8.44 (d, 1 H), 7.90 (d, 1 H), 7.72 (d, 2 H), 7.52 (m, 2 H), 7.41-3.33 (m, 6 H), 7.22 (t, 1 H), 7.15-7.11 (m, 3 H), 6.96 (d, 1 H), 4.43 (dd, 1 H), 4.25 (dd, 1 H), 3.99 (m, 1 H), 3.17 (d, 2 H), 2.52 (s, 3 H); MS (M+H): 590.4.

Example 27

Prepatation of *N*-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}cyclohexanecarboxamide

Following the procedure of Example 25, except substituting cyclohexane carbonyl chloride for benzoyl chloride, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.40 (d, 1 H), 7.70 (s, 1 H), 7.65 (s, 2 H), 7.43-7.36 (m, 7 H), 7.14 (t, 1 H), 7.09 (d, 1 H), 6.90 (d, 1 H), 4.12 (d, 1 H), 4.26 (d, 1 H), 3.98 (m, 1 H), 3.17 (d, 2 H), 2.51 (s, 1 H), 2.29 (m,1 H), 1.80 (m, 4 H), 1.47-1.28 (m, 6 H); MS (M+H):560.4.

Example 28

Preparation of [(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting 2-furanylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.47(d, 1 H), 8.03(s, 1 H), 7.80(d, 1 H), 7.66(d, 1 H), 7.45-7.20(m, 11 H), 7.18(dd, 1 H), 6.85(d, 1 H), 6.61(dd, 1 H), 4.43(dd, 1 H), 4.29(dd, 1 H), 3.99-3.07(m, 1 H), 3.18(d, 2 H); MS (M+H): 487.4.

Example 29

Preparation of {(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine

Following the procedure of Example 23(a)-23(c), except substituting 2-thienylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.45(d, 1 H), 7.88(s, 1 H), 7.75(d, 1 H), 7.48-7.15(m, 14 H), 4.44(dd, 1 H), 4.28(dd, 1 H), 3.97-3.90(m, 1 H), 3.18(d, 2 H); MS (M+H): 503.2.

Example 30

Preparation of [(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting 3-furanylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.48(d, 1 H), 7.93(d, 1 H), 7.85(s, 1 H), 7.77(d, 1 H), 7.64(s, 1 H), 7.46(d, 1 H), 7.44-7.25(m, 9 H), 7.22(dd, 1 H), 6.82(d, 1 H), 4.46(dd, 1 H), 4.30(dd, 1 H), 4.28-4.25(m, 1 H), 3.19(d, 2 H); MS (M+H): 487.4.

Example 31

Preparation of [(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine

Following the procedure of Example 23(a)-23(c), except substituting 3-thienylboronic acid for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.46(d, 1 H), 7.87(d, 1 H), 7.82(s, 1 H), 7.67(d, 1 H), 7.58(s, 1 H), 7.44(d, 1 H), 7.44-7.25(m, 10 H), 7.22(dd, 1 H), 4.45(dd, 1 H), 4.31(dd, 1 H), 4.28-4.25(m, 1 H), 3.18(d, 2 H); MS (M+H): 503.2.

Example 32

Preparation of 3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol

Following the procedure of Example 1(a)-1(f), except substituting 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for phenylboronic acid, the title compound was prepared. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.42(d, 1 H), 7.81(s, 1 H), 7.68(d, 1 H), 7.42-7.33(m, 6 H), 7.14-7.11(m, 2 H), 6.78-6.72(m, 3 H), 4.44(dd, 1 H0, 4.29(dd, 1 H), 3.99-3.97(m, 1 H), 3.18(d, 2 H), 2.52(s, 3 H); MS (M+H): 451.2.

Example 33

Preparation of [(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

a) 5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl trifluoroacetate

To a solution of the compound of Example 16(a) (33mg, 0.076mmol) in EtOAc was added Me_3OBF_4 (17mg, 0.115mmol) and stirred for 3h at rt. The reaction was completed indicated by LC/MS. Aqueous $NaHCO_3$ was added. Organic layer was separated and concentrated, and the residue was purified by flash column chromatography (hexane/EtOAc 2:1) to give a white foaming solid (14.7 mg , 43%).

b) 5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinol

To a solution of the compound of the Example 33(a) (14.7mg, 0.033mmol) in 0.5ml MeOH was added 2N NaOH 0.1 mL. The resulting mixture was stirred at rt for 30 min and concentrated. The residue was dissolved in 1 mL of water and neutralized with HOAc. The resulting mixture was extracted by CH_2Cl_2 (5 mL X 3). The organic layers were combined and concentrated, and the residue was purified by flash column chromatography (Hexane/ EtOAc 1:1) to give a white solid (10 mg).

c) 1,1-dimethylethyl [(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]carbamate

DEAD (10.4 uL, 0.066 mmol) was added to a solution of the compound of Example 33(b) (10.8 mg, 0.033 mmol), compound of Example 1 (a) (12.4 mg, 0.049 mmol) and Ph_3P (13.0 mg, 0.049 mmol) in THF (2 mL) at rt. The resulting mixture was stirred at rt overnight. Excess of DEAD and Ph3P were added. The reaction mixture was concentrated and the residue was purified by flash column chromatography (CH_2Cl_2/EtOAc 1:1) to give a white solid (100mg, coeluted with $Ph_3P=O$).

d) [(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine

A solution of the compound of Example 33(c) and 0.2 mL of TFA in CH_2Cl_2 (0.8 ml) was stirred at room temperature for 20 min, diluted with toluene and concentrated. The residue was taken up into DMSO and purified on reversed phase HPLC (MeCN, H_2O, 0.1% TFA) to give a white solid (4.5mg, 20% over 3 steps). ^1H NMR (CD_3OD, 400 MHz) δ 8.52 (d, 1H), 7.99 (d, 1H), 7.66 (s, 1H), 7.42-7.31 (m, 11H), 7.01 (d, 1H), 4.48 (dd, 1H), 4.33 (dd,1H), 4.12 (s, 3H), 4.02-3.99 (m, 1H), 3.19 (d, 2H), 2.62 (s, 3H); MS (M+H): 449.2

Example 34 Capsule Composition

An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

Table I

INGREDIENTS	AMOUNTS
(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 35 - Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.5% by weight of (S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine in 10% by volume propylene glycol in water.

Example 36 - Tablet Composition

The sucrose, calcium sulfate dihydrate and an Akt inhibitor as shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid;, screened and compressed into a tablet.

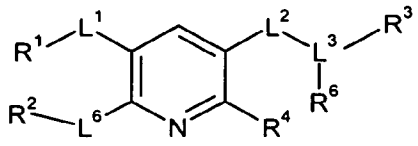
Table II

INGREDIENTS	AMOUNTS
(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

L^1 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

L^2 is selected from the group consisting of a bond, -O-, -N(R^5)-, -N(R^5)C(O)-, -S-, -S(O)-, -S(O_2)-, and -C(O)N(R^5)-;

L^3 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

L^6 is selected from the group consisting of a bond, -O-, -N(R^5)-, -S-, -S(O)-, -S(O_2)-, alkyl, and -N(R^5)C(O)-;

R^1 is selected from the group consisting of aryl, substituted aryl, heterocycle and substituted heterocycle;

R^2 is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR^7, -C(O)NR^8R^9, -S(O)$_2$NR^8R^9, and -S(O)$_n$$R^7$,

where n is 0-2,

R^7 is hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and

R^8 and R^9 are independently hydrogen, cycloalkyl, C_1-C_{12}aryl, substituted cycloalkyl, substituted C_1-C_{12}aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^{10}$, $-S(O)_nR^{10}$, $-C(O)NR^{10}R^{11}$, $-S(O)_2NR^{10}R^{11}$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, and substituted aryl,

or R^8 and R^9 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally subtituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^{10} and R^{11} are independently hydrogen, alkyl, cycloalkyl, C_1-C_{12}aryl, substituted alkyl, substituted cycloalkyl and substituted C_1-C_{12}aryl, and n is 0-2;

R^3 and R^6 are independently selected from the group consisting of hydrogen, aryl, substituted aryl, and arylalkoxy; provided that when L^1 and L^2 are bonds, at least one of R^3 and R^6 is other than hydrogen;

R^4 is selected from the group consisting of hydrogen and halo; and

R^5 is selected from the group consisting of hydrogen and alkyl.

2. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (I), as described in claim 1.

3. The compound of Formula (I), as claimed in claim 1, wherein

L^1 is selected from the group consisting of a bond, -O-, $-N(R^5)$-, -S-, -S(O)-, $-S(O_2)$-, alkyl, and $-N(R^5)C(O)$-;

L^2 is selected from the group consisting of a bond, -O-, $-N(R^5)$-, $-N(R^5)C(O)$-, -S-, -S(O)-, $-S(O_2)$-, and $-C(O)N(R^5)$-;

L^3 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

L^6 is a bond;

R^1 is selected from the group consisting of aryl, substituted aryl, heterocycle and substituted heterocycle;

R^2 is selected from, cycloalkyl and substituted cycloalkyl;

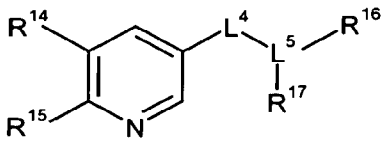
R^3 and R^6 are independently selected from the group consisting of hydrogen, aryl, substituted aryl, and arylalkoxy; provided that when L^1 and L^2 are bonds, at least one of R^3 and R^6 is other than hydrogen;

R^4 is selected from the group consisting of hydrogen and halo; and

R^5 is selected from the group consisting of hydrogen and alkyl.

4. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (I), as described in claim 3.

5. A compound of Claim 1 represented by the following Formula (II):



(II) (II)

wherein:

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, C_1-C_{12}aryl and C_1-C_{12}aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl and substituted C_1-C_{12}aryl.

6. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (II), as described in claim 5.

7. A compound of Formula (II), as described in claim 5:
wherein

L^4 is selected from the group consisting of a bond, and -O-;

L^5 is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

R^{14} is selected from the group consisting of C_1-C_{12}aryl, and substituted C_1-C_{12}aryl;

R^{15} is selected from cycloalkyl and substituted cycloalkyl; and

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_{12}aryl and substituted C_1-C_{12}aryl.

8. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (II), as described in claim 7.

9. A method of treating or lessening the severity of a disease or condition selected from cancer and arthritis, wherein said method comprises the administration of an effective amount of a compound of Formula I, as described in claim 1.

10. A method of treating or lessening the severity of a disease or condition selected from cancer and arthritis, wherein said method comprises the administration of an effective amount of a compound of Formula I, as described in claim 2.

11. The method according to claim 9 wherein said cancer is selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

12. The method according to claim 10 wherein said cancer is selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

13. A compound selected from:

(S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-furan-2-yl-5-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5,6-bis-(3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-thiophen-2yl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(4-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(3-chlorophenyl)-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-benzyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopent-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopentyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohex-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclohexyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(piperidin-4-ylmethoxy)-pyridin-3-yl]-1H-indazole;

3-[5-(3-Methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-propylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-thiophen-2-yl)-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) –6-(5-methyl-furan-2-yl)-pyridin-3-yloxy]-ethylamine;

3-Methyl-5-[2-phenyl-5-(4-pyridin-3-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

3-Methyl-5-[2-phenyl-5-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;

[(1*S*)-2-{[6-(3-furanyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(5-chloro-2-thienyl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-{[6-(3-aminophenyl)-5-(3-methyl-1*H*-indazol-5-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

(S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-{6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) - pyridin-3-yloxy}-ethylamine;

(S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

[(1*S*)-2-{[5-(3-methyl-1*H*-indazol-5-yl)-6-(1*H*-pyrrol-2-yl)-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine;

N-{3-[5-{[(2S)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}benzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}-2,6-difluorobenzamide;

N-{3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenyl}cyclohexanecarboxamide;

[(1*S*)-2-({5-[3-(2-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

{(1*S*)-2-phenyl-1-[({6-phenyl-5-[3-(2-thienyl)-1*H*-indazol-5-yl]-3-pyridinyl}oxy)methyl]ethyl}amine;

[(1*S*)-2-({5-[3-(3-furanyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

[(1*S*)-2-({5-[3-(3-thienyl)-1*H*-indazol-5-yl]-6-phenyl-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;

3-[5-{[(2*S*)-2-amino-3-phenylpropyl]oxy}-3-(3-methyl-1*H*-indazol-5-yl)-2-pyridinyl]phenol; and

[(1*S*)-2-{[5-(2,3-dimethyl-2*H*-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy}-1-(phenylmethyl)ethyl]amine.

14. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (II), as described in claim 13.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 1.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 2.

17. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier or diluent and an effective amount of a compound of Formula (I) as described in claim 1, which process comprises bringing the compound of Formula (I) into association with the pharmaceutically acceptable carrier or diluent.

18. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier or diluent and an effective amount of a compound of Formula (I) as described in claim 2, which process comprises bringing the compound of Formula (I) into association with the pharmaceutically acceptable carrier or diluent.

ABSTRACT OF THE DISCLOSURE

Invented are novel pyridine compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.